Lyophilization of Pharmaceuticals I

Effect of Certain Physical-Chemical Properties

By PATRICK DeLUCA and LEON LACHMAN

In this study, a specially designed low-conductance bridge was employed for the determination of eutectic temperatures by electrical resistivity. This method has been found to be more reliable than the usually employed temperature-time measurements. The bridge consists of four wide-range decades and eight narrow-range decades from $0-10^{12}$ ohms. An X-Y recorder was used for plotting the conductance as a function of temperature. A specially fabricated chamber, designed to function at controlled pressures, was employed for the eutectic measurements. Eutectic temperatures for a series of organic salts have been found to be considerably higher than values previously believed. The eutectics for these particular compounds varied from $-0.75°$ to $-12°$. A mathematical expression has been developed, illustrating the relationship between the eutectic temperature and the solubility parameter. Calculated values agree favorably with the experimental values for a series of organic salts. Mannitol and lactose have little or no effect on the solubility or eutectic temperature of the various agents studied. Utilization of data such as these has been found to be extremely valuable in the design of lyophilization cycles.

LYOPHILIZATION is the term given to the process of freeze drying, whereby ice is sublimed from frozen solutions, leaving a dry porous mass of approximately the same size and shape as the original frozen mass. The resulting product is in a stable form and can be redissolved rapidly in water.

The technique of lyophilization is employed for injectable pharmaceuticals exhibiting poor stability in solution. The process consists of dissolving the substance or substances in water, sterilizing the solution by passage through a bacterial filter, filling into individual containers, then removing the water as vapor from the frozen state. In this manner, a compound that is heat sensitive and undergoes rapid decomposition in aqueous solution can be formulated into a stable injectable form. Under the proper conditions, freeze drying gives a stable, rapidly soluble, and elegant injectable preparation.

A discussion of freeze drying requires frequent reference to the eutectic point of the material being dried. The eutectic temperature governs the temperature at which a sample must be held during freeze drying for sublimation to occur from the solid state. For this reason, one of the most important factors in freeze drying is the regulation of the temperature of the product during the course of drying. The temperature must be sufficiently low to prevent any melting of the frozen mass and sufficiently high to allow the lyophilization process to be completed within a reasonable time.

In many cases a lyophilization cycle is developed without any eutectic measurements, but instead by trial and error using repeated experiments under different conditions. Although an adequate cycle for a given product is usually obtained, this procedure constitutes a loss of both time and money and does not give the assurance that an optimum cycle has been developed. As a result of this practice, pharmaceutical products are routinely frozen to $-35°$ or lower, then dried. In the event that the eutectic temperature is well above $-35°$, the commencement of drying at such a low temperature would result in the expenditure of unnecessary time and cost.

The purpose of this investigation was to endeavor to place the design of lyophilization cycles on a more scientific basis through a knowledge of certain physical-chemical parameters, such as eutectic temperature and solubility. Factors influencing these parameters—namely, salt type, concentration, diluent, and pressure—were evaluated. The equipment designed for accurate measurement of the eutectic temperature also is described.

THEORETICAL

The sublimation of pure ice and the evaporation of water from a frozen mixture proceed only when the partial pressure of water vapor at a frozen surface is greater than that at any other point close to it (1, 2). In a closed system at reduced pressure, the accumulation of water vapor in the enclosure retards evaporation due to collision between evaporating molecules and those of the surrounding air. As the concentration of evaporated water vapor increases, so does the probability that for every molecule leaving the frozen mass one will return. Equilibrium is finally attained, and drying ceases
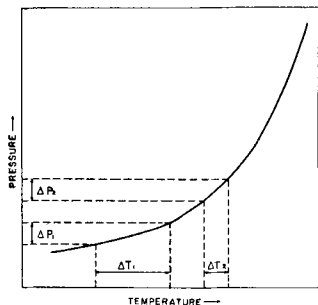
Fig. 1.—Variation in pressure with temperature.

when the vapor becomes saturated throughout the enclosure; any initial temperature difference between the evaporating source and ambient air then disappears. Complete cessation of drying is prevented when some means of removal of moisture from the system is provided. However, the removal of water vapor from the surface of the sample at constant temperature may be limited by the diffusion of the vapor to the moisture removing agent.

Three general methods which have been employed for the removal of water vapor are: (*a*) condensation at low temperature, (*b*) combination with a desiccating agent, and (*c*) direct pumping.

The most commonly employed method in pharmaceutical practice is condensation at low temperatures. If a cold surface is introduced into a vacuum system at a temperature below that of the sample, the water vapor evolved by the drying material will be condensed as ice on this refrigerated surface. The nearer the temperature of the condenser is to the drying temperature, the more slowly will drying proceed. However, considering the temperature alone may produce an inaccurate impression, for the important factor is the vapor pressure difference between the two surfaces. The "driving force" which governs the rate of sublimation is the difference in the vapor pressure of the substance and that of the condenser.
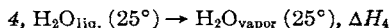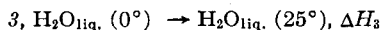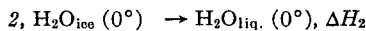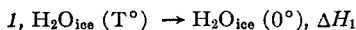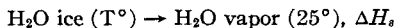
The rate of sublimation or, as previously expressed by Greaves (3), the rate of flow, is a function of vapor pressure difference and the resistance to vapor flow:

$$\frac{\text{(driving force)}}{\text{resistance to flow}} \begin{array}{c}\text{vapor pressure difference} \\ \hline \text{resistance to flow}\end{array} = \text{rate of flow}$$

Vapor pressure is related to temperature, but the relationship is more nearly logarithmic than linear. As illustrated in Fig. 1, at low temperatures, in order to establish a substantial difference in vapor pressure, a large temperature difference is necessary; while at higher temperatures, the same vapor pressure difference can be attained with a considerably smaller difference in temperature. Although low partial pressures of air and water vapor provide conditions favorable to drying, they do not promote it, and without a supply of latent heat to maintain a driving force, the rate of evaporation would diminish. This may be explained on the basis that the rate of evaporation is a function of the average velocity of the water molecules. As the molecules having the highest velocities escape, the average velocity of those remaining is lowered. Since the average velocity of the molecules is a function of temperature, a lowering of the average

velocity would result in a lowering of temperature. Consequently, to maintain an efficient rate of evaporation, it is necessary to apply heat continually.

Although drying by sublimation is carried out under high vacuum, the latent heat of sublimation of ice exceeds the latent heat of evaporation of water. Thermodynamically, the energy required to sublime a quantity of ice at any given temperature to produce vapor at room temperature is equivalent to the heat required to raise the temperature of the ice to the freezing point, plus the heat of fusion, plus the heat necessary to raise the temperature of the liquid to room temperature, plus the heat of vaporization. This may be illustrated by

$$H_2O \text{ ice } (T°) \rightarrow H_2O \text{ vapor } (25°), \Delta H_s$$

$$1, H_2O_{ice} (T°) \rightarrow H_2O_{ice} (0°), \Delta H_1$$

$$2, H_2O_{ice} (0°) \rightarrow H_2O_{liq.} (0°), \Delta H_2$$

$$3, H_2O_{liq.} (0°) \rightarrow H_2O_{liq.} (25°), \Delta H_3$$

$$4, H_2O_{liq.} (25°) \rightarrow H_2O_{vapor} (25°), \Delta H_4$$

$$\Delta H_s = \Delta H_1 + \Delta H_2 + \Delta H_3 + \Delta H_4$$

The faster heat can be supplied, the faster drying can be carried on, but the temperature of the product must not be allowed to rise above its liquefying point. Efficient vacuum pumps should be used to maintain a relatively constant temperature during drying. If a sufficiently low pressure is not maintained, the temperature of the product will rise until a eutectic separation occurs, and an apparent partial softening or puffing of the product may result.

The area of physical chemistry covering the process of lyophilization is called "phase rule." A brief review of some of the very basic principles of phase rule may be advantageous in developing an understanding of drying from the frozen state.

On examination of Fig. 2, it can be seen readily that water boils at 100° when the atmospheric pressure is 760 mm. Hg or, expressed in another way, the vapor pressure of water at 100° is 760 mm. Hg. If the pressure above the water is progressively lowered, the boiling point of the water also will be lowered so that it may be boiled at temperatures well below 100°. Water at temperature T_A can be evaporated by lowering the pressure to P_A. At point B, water exists in equilibrium with ice and water vapor. The vapor pressure above the ice and solution at this point is approximately 4 mm. Hg. If pressure is applied to the system, the vapor and ice will liquefy, and a lower temperature will be required to freeze the water. Conversely, if the pressure is lowered, vaporization will
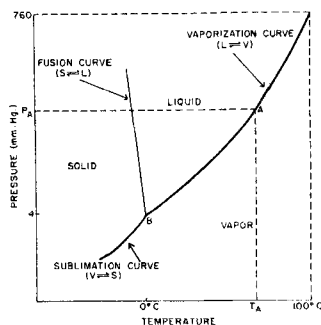

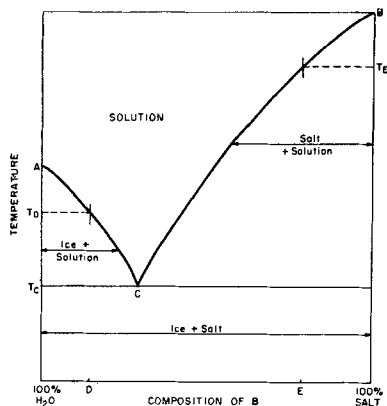Fig. 2.—Vapor pressure phase curve for water.

Fig. 3.—Phase equilibrium diagram for a salt in water.

occur, causing a cooling of the system. If the temperature of the system at B is lowered, the liquid phase disappears, and the vapor pressure above the ice is reduced. The corresponding values of temperature and pressure can be obtained readily from the sublimation curve. If the vapor pressure of a closed system is lowered to a value below that on the sublimation curve, sublimation will occur.

Figure 3 represents a simple two-component system of a salt in water where the solid phases are pure components. The freezing point of pure water is designated by A; B corresponds to the melting point of pure salt. If a quantity of salt is added to water so that a composition corresponding to D results, the freezing point of water will be depressed to a temperature T_D. If this solution is cooled further, ice will continue to crystallize out, and the solution will become more and more concentrated. At point C, a temperature is reached where both ice and salt will crystallize out in a mixture.

If water is added to pure salt, and a composition corresponding to E results, the temperature of the solution will have to be lowered to cause pure salt to crystallize from solution. If the temperature is lowered continually, pure salt will continue to precipitate, and the solution will become more and more dilute until once again a composition is reached where both salt and ice crystallize out in a mixture. From this figure, curve BC can be designated as the solubility curve of B in water and curve AC as the solubility curve of ice in liquid B. However, curve AC is recognized more readily as the freezing point curve of water at various concentrations of salt. The eutectic point C is clearly seen to be the point of intersection of the solubility curve of the salt and the freezing point curve of water.

Mathematical Relationship Between Solubility and Eutectic Temperature.—Using the Clapeyron–Clausius equation and applying Raoult's law, the general form of the equation at constant pressure which can be used for expressing both the depression of the freezing point and the solubility of the pure solid is

$$\ln X = -\frac{Lf}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right) \qquad \text{(Eq. 1)}$$

where X = the mole fraction of the phase separating, Lf = the heat of fusion of the solid phase, and T_0 = the melting point of the solid phase.

For a salt, x, in solvent, y, the freezing point depression equation becomes

$$\ln y = -\frac{Lf}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right) \qquad \text{(Eq. 2)}$$

where Lf = heat of fusion, R = gas constant, T_0 = melting point of solvent, and T = freezing point.

The solubility equation can be represented as

$$\ln x = -\frac{Lf'}{R}\left(\frac{1}{T'} - \frac{1}{T_0'}\right) \qquad \text{(Eq. 3)}$$

where Lf' = differential heat of solution, T' = temperature, and T_0' = melting point of pure salt. Since y is the mole fraction of solvent separating and $x + y = 1$, then $(1 - x)$ can be substituted for y in Eq. 2.

$$\ln(1 - x) = -\frac{Lf}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right) \qquad \text{(Eq. 4)}$$

In order to proceed, an approximation is introduced at this point. For values of x, 0.1 or lower, $\ln(1 - x) \cong -x$. Therefore

$$x = \frac{Lf}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right) \qquad \text{(Eq. 5)}$$

Expressing the solubility Eq. 3 in exponential form

$$x = e^{-\frac{Lf'}{R}\left(\frac{1}{T'} - \frac{1}{T_0'}\right)} \qquad \text{(Eq. 6)}$$

Since the eutectic for an invariant system occurs at the point of intersection of the freezing point depression curve and the solubility curve, it is possible to derive an expression for eutectic temperature or concentration by combining Eqs. 5 and 6.

$$\frac{Lf}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right) = e^{-\frac{Lf'}{R}\left(\frac{1}{T'} - \frac{1}{T_0'}\right)} \qquad \text{(Eq. 7)}$$

Replacing the exponential and substituting the eutectic temperature, T_e, for T and T',

$$\log\left[\frac{Lf}{R}\left(\frac{1}{T_e} - \frac{1}{T_0}\right)\right] = -\frac{Lf'}{2.303\,R}\left(\frac{1}{T_e} - \frac{1}{T_0'}\right) \qquad \text{(Eq. 8)}$$

By rearranging terms in Eq. 8, the following expression results:

$$\log\left(\frac{1}{T_e} - \frac{1}{T_0}\right) = -\frac{Lf'}{2.303\,R}\left(\frac{1}{T_e} - \frac{1}{T_0'}\right) - \log\frac{Lf}{R} \qquad \text{(Eq. 9)}$$

For water as the solvent, the following substitutions can be made

$$Lf = 1436 \text{ cal./mole}$$
$$T_0 = 273.1°K$$
$$R = 1.9869 \text{ cal. degree}^{-1} \text{ mole}^{-1}$$

$$\log\left(\frac{1}{T_e} - 0.0036616\right) =$$
$$-\frac{Lf'}{(4.5758)}\left(\frac{1}{T_e} - \frac{1}{T_0'}\right) - 2.8590 \qquad \text{(Eq. 10)}$$

The eutectic temperature,[1] T_e, is a function of

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[1] The numerical estimation of the eutectic temperatures in the implicit function was programmed in Fortran II for the IBM 1401 (8K).
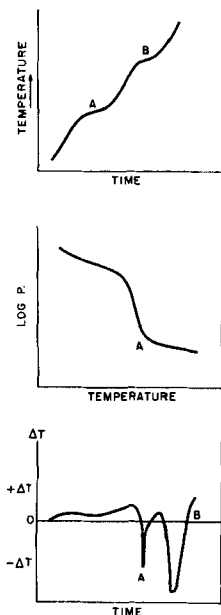
Fig. 4.—Curves obtained for the various methods employed in the determination of eutectic temperature. Thermal analysis (top); electric resistivity (middle); differential thermal analysis (bottom). Key: A, eutectic point; B, freezing point.

the Lf' value for the material and its melting point, T_0'. For the present, the Lf' value[2] will be defined as the "heat effect accompanying solution."

Determination of Eutectic Points.—In practice it is usually more convenient, in order to avoid any difficulty from supercooling or uneven cooling, to measure the eutectic temperature by progressive warming of the material which has been frozen below its eutectic point.

Several methods have been employed for the determination of eutectic points. Among these are: (*a*) thermal analysis, (*b*) differential thermal analysis (4), and (*c*) electric resistivity (5).

The curves obtained for each of these methods are illustrated in Fig. 4. In the first curve, the temperature is plotted against time. Plateau *A* is caused by the melting of the eutectic mixture at the eutectic temperature and Plateau *B* results from the thawing of ice. Unfortunately, the curves obtained in practice usually do not occur so dramatically, especially when more than one salt is included in the formulation. The differential thermal analysis technique has been employed to increase the sensitivity of the direct thermal analysis method. This involves thermal measurement of a sample and direct comparison with a reference solution under the same conditions. A typical curve is shown in the bottom plot, where the temperature difference between sample and reference is plotted as a function of time.

A more accurate method for determining eutectic temperature would be by electrical resistivity. This method consists of measuring the resistance of a frozen sample as a function of temperature. As illustrated in the center graph, below the eutectic

temperature, the resistance of the frozen mass is very high. When the eutectic temperature is reached, there will be a sudden change in resistivity due to a phase change and the occurrence of liquid in the mass.

EXPERIMENTAL

Equipment.—Since it was the authors' experience that methods based upon temperature measurements alone were susceptible of giving nonreproducible results, a specially designed low-conductance bridge was employed for the determination of eutectic temperature by electrical resistivity. The influence of concentration, salt type, and diluents on the eutectic temperature was evaluated using this equipment.

Figure 5 shows the equipment employed for the eutectic measurements. In the far right of the photo is the specially designed Plexiglas chamber used for housing and cooling the conductivity cell. Samples were cooled by passing liquid carbon dioxide through the housing holding the conductivity cell and permitting it to expand. By this method, samples were cooled to below $-30°$ in approximately 5 min. The chamber is designed to permit studies at ambient or reduced pressures.

The conductivity bridge is capable of measuring resistances as high as 10^{12} ohms. It consists of four wide-range decades ranging from $0–10^6$ ohms to $0–10^{12}$ ohms and eight narrow-range decades from $10^4–10^5$ ohms to $10^{11}–10^{12}$ ohms. An additional bridge is included to act as an internal standard. A thermocouple or a thermistor probe is used to sense changes in temperature of the material in the conductivity cell. The *x-y* recorder is employed for plotting the resistivity as a function of temperature. This temperature-conductivity bridge was designed for maximum versatility by providing a means for selecting the desired axis on the recorder for a particular measurement. For example, resistance *versus* thermocouple, resistance *versus* thermistor, and thermistor *versus* thermocouple can be plotted on either axis.

The conductivity cell is illustrated in Fig. 6. Two platinum electrodes, a thermistor, and a grounded thermocouple are inserted through a Teflon cap into the vial. In addition, a vent is provided in the cap to maintain a pressure balance within the cell.

Eutectic Measurements.—Three milliliters of a freshly prepared solution were filled into a 10-ml. sample cell, and the electrode assembly was inserted in a way so that the platinum electrodes and

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[2] The Lf' value was determined from solubility measurements as a function of temperature using the expression for solubility

$$\ln x = -\frac{Lf'}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)$$

and plotting log *x versus* $1/T$. Lf' is calculated from the slope of the line which is equal to $-Lf'/2.303\,R$.

Fig. 5.—Equipment employed for measuring resistivity as a function of temperature.
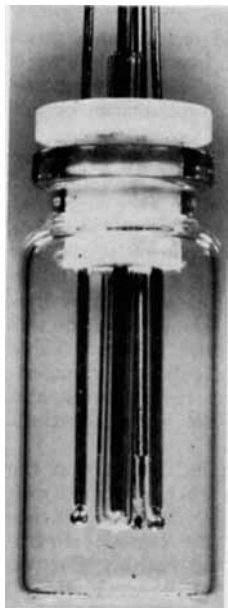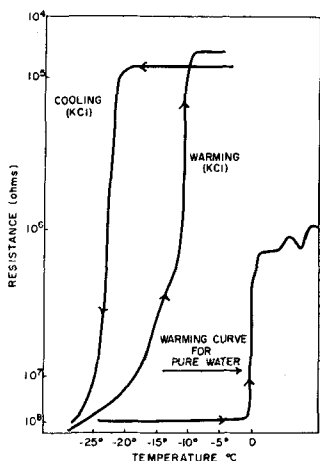
Fig. 6.—Conductivity cell employed for measuring resistivity as a function of temperature.

Fig. 7.—Cooling and warming curves for a 3 molal potassium chloride solution (0–10⁸ ohm decade).

For this run, the wide-range 0–10⁸ ohm decade was employed. As can be seen, there is a vast difference between the cooling and warming curves due to supercooling during freezing. In the event the cooling curve was used to measure eutectic temperature, inaccurate information would be obtained as a result of the supercooling effect. The eutectic temperature can be obtained from the break in the warming curve which is caused by a sudden tenfold decrease in resistivity. For potassium chloride, eutectic melting occurred at −11.1°.

The sharpness of the change of resistivity at the eutectic temperature can be increased by employing the narrow range decades of the instrument. However, since each narrow range decade is full scale on the x-y recorder, it is necessary to plot the log of the resistivity *versus* the temperature to present the complete curve of the relationship between resistance and temperature. The curves in Fig. 8 show such a plot for the three electrolytes—potassium chloride, sodium chloride, and potassium bromide. The eutectic temperature for sodium chloride was found to be deepest, occurring at −21.6°. The eutectic temperature was found to be −12.9° for potassium bromide and −11.1° for potassium chloride.

The relationship between eutectic temperature and solubility is illustrated by the curves in Fig. 9 which show the effect of temperature on the molal concentration of electrolyte. The heat effect accompanying solution is very small for sodium chloride, compared to potassium bromide and po-
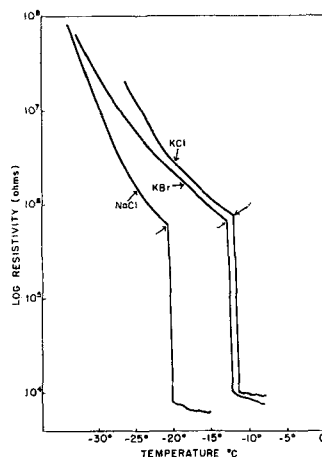

Fig. 8.—Determination of eutectic temperature by plotting log resistivity as a function of temperature. Values at indicated points on curves are:
NaCl, −21.6°;
KBr, −12.9°;
KCl, −11.1°.

thermistor or thermocouple were just below the surface of the liquid. The solution was frozen to −35° by allowing the carbon dioxide to expand into the housing holding the conductivity cell in the chamber. The sample was then allowed to warm gradually, and the electrical resistance was plotted as a function of temperature on the x-y recorder.

Solubility Studies.—The solubilities were measured at 7°, 17°, and 30° for each of the organic electrolytes studied. Nitrogen-flushed saturated solutions were filled into 20-ml. ampuls and allowed to come to equilibrium at the desired temperature. The phase solubility technique (6) was employed in some cases so that a measure of the purity of the materials employed could be determined.

RESULTS AND DISCUSSION

Inorganic Salts.—The plots in Fig. 7 illustrate the cooling and warming curves obtained for a 3.0 molal solution of potassium chloride. The warming curve for pure water is included as a reference.
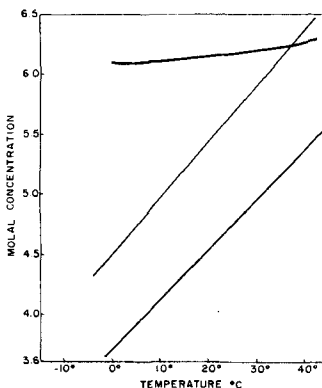

Fig. 9.—Effect of temperature on the solubility of several electrolytes. (Eutectic temperature is in parentheses.) Top curve: NaCl (−21.6°); middle curve: KBr (−12.9°); lower curve: KCl (−11.1°).
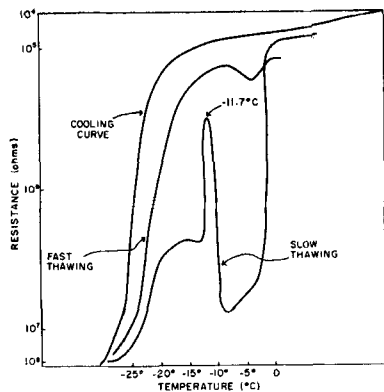
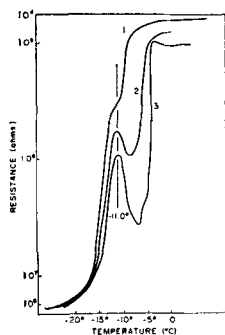Fig. 10.—Cooling and warming curves for a 0.3 molal methylphenidate HCl solution (0–10⁸ ohm decade).

Fig. 11.—Effect of concentration on the warming curves for phentolamine methanesulfonate solutions (0–10⁸ ohm decade). Key: 1, 4.05 molal; 2, 1.22 molal; 3, 0.50 molal.

tassium chloride, as evidenced by the slight change in solubility with temperature. It would appear that a soluble substance showing little change in solubility with change in temperature will have a deeper eutectic point than a substance for which the solubility varies significantly with temperature change, as substantiated by the experimental data reported here.

Organic Salts.—The curves obtained for the organic electrolytes are somewhat more complex than those obtained for the inorganics. Two factors contributing to the complexity are (*a*) the sensitivity of the equipment and (*b*) possible electrode effects. Nevertheless, the eutectic point can be determined from the sudden change in resistivity, indicating a phase transition. The curves in Fig. 10 show the freezing and thawing curves for methylphenidate hydrochloride. In one case, the mass was allowed to thaw rapidly by removing the conductivity cell from the cup in the chamber. In this way, the sample temperature rose from −35° to −2° in about 20 min. For slow warming, a similar temperature change required 1.5–2 hr.

From these curves it is evident that rapid warming masks the eutectic point. One possible explanation for this behavior is that the response of the recorder to the signals of the sensing element is not rapid enough to overcome any overlapping effect. Another explanation may be that the rapid temperature change swamps the endothermic reaction occurring at the eutectic point.

The plots in Fig. 11 show the effect of concentration on the conductance of phentolamine methanesulfonate solutions. Curve 1 represents the most

concentrated solution saturated and precipitated during freezing. As one would expect for a saturated solution, the eutectic and freezing points were found to be quite similar. The eutectic temperature for phentolamine methanesulfonate occurs at −11°.

To determine the utility of Eq. 10 for estimating eutectic temperature from a knowledge of Lf' and melting point, the calculated values were compared with those obtained experimentally. An example of a determination of Lf' from a plot of log x versus $1/T$ is illustrated in Fig. 12 for methylphenidate hydrochloride. Since the solubility was measured at only three temperatures, the slope of the line was determined by the method of least squares. Table I shows a comparison of the calculated and experimentally determined eutectic temperatures and related solubility data for the pharmaceuticals studied.

It is evident from the data in Table I that the diluents mannitol and lactose, when combined with methylphenidate hydrochloride, do not influence the eutectic temperature of the organic electrolyte. In addition, neither agent had an effect on the solubility of methylphenidate hydrochloride.

The data in this table appear to show a relationship between solubility and the eutectic temperature; the more soluble salts generally displayed the lower eutectic temperatures. The calculated eutectic temperatures in most cases show a close correlation with the experimentally determined values. This is an indication that the equation can be of considerable value in estimating the eutectic temperature where sensitive equipment is not available for precise measurement. It is necessary to remember, however, that the equation is valid only where the heat effect is constant down to the eutectic point. Deviation such as that observed for sodium chloride may be explained on the basis that the heat effect in the vicinity of the eutectic differs from that at higher temperatures, where measurements are normally made.

The reason for the apparently more soluble methylphenidate phosphate having a higher eutectic temperature than the corresponding hydrochloride
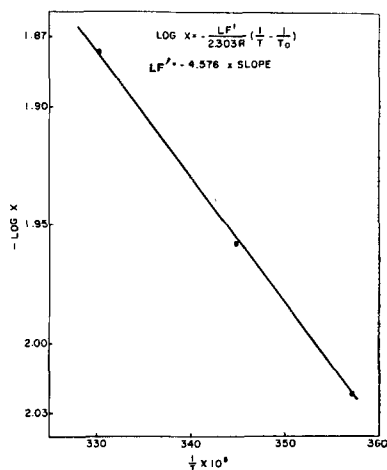

Fig. 12.—Determination of Lf' from a plot of the log mole fraction of methylphenidate hydrochloride against the reciprocal of the absolute temperature.

TABLE I.—EUTECTIC TEMPERATURE AND SOLUBILITY DATA

| Compd.	M.p., °C.	Molal Solubility at 30°C.	Lf', cal./mole	Eutectic Temp., °C. Exptl.	Calcd.
Methylphenidate					
Hydrochloride	211	0.749	2450	−11.7	−11.39
Methanesulfonate	191	4.85	2972	−10.1	−8.77
Phosphate	178	1.953	4324	−4.29	−3.92
Phentolamine					
Hydrochloride	240	0.0645	4310	−1.3	−2.34
Methanesulfonate	179	3.979	3170	−11.0	−8.28
Phosphate	191	0.120	6233	−0.75	−0.88
Mannitol N.F.	167	1.0		−2.24	
Lactose U.S.P.	201	0.6		−5.40	
Methylphenidate HCl with mannitol		0.755		−11.7	
Methylphenidate HCl with lactose		0.761		−11.9	
Sodium chloride	801	6.21	101.1	−21.6	−64.76
Potassium chloride	776	4.97	1455	−11.1	−12.03
Potassium bromide	750	5.93	1431	−12.9	−12.72
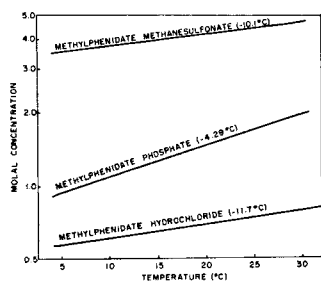
Fig. 13.—Solubility of some salts of methylphenidate as a function of temperature.

salt can best be explained by the relationship between temperature and solubility which is demonstrated in Fig. 13. Although the data in Table I show that the phosphate salt is more than twice as soluble as the hydrochloride salt at 30°, the heat effect accompanying dissolution of the phosphate is larger than the hydrochloride, evidenced by the steeper slope. Consequently, the solubility decreases markedly with decrease in temperature, which in turn results in a higher eutectic point for the phosphate salt.

The plots in Fig. 14 show the effect of temperature on the solubility for the three salts of phentolamine. The considerably greater solubility and lower heat effect of the methanesulfonate salt are responsible for the lower eutectic point, compared with the other salts.

Effect of Reduced Pressure on the Eutectic Temperature.—Since the process of freeze drying is carried out at low partial pressures of air, it seemed advisable to investigate the behavior of a two-component system under reduced pressure. McKay and Higman (7) in a study on the effect of increased pressure on eutectic temperature and composition for some two-component nonaqueous systems found that a 1000-fold increase in pressure caused a significant elevation of the eutectic temperature. However, these systems were not investigated at reduced pressures. For methylphenidate HCl under reduced pressure, the eutectic temperature was found to be in the range of −11.7° to −12.4°. It appears, therefore, that the eutectic temperature is not significantly affected by a reduction in pressure. This observation is in accord with phase rule theory.

Application of Information to a Production Cycle.—The eutectic temperature for a lyophilized product

routinely processed in production was found to be considerably higher by electrical resistivity measurements than that previously determined by the thermal method. This discrepancy was due to the less accurate estimate of the eutectic point obtained from freezing curves. Tables II and III show a comparison of the cycle which has been used for the last 5 years and the new cycle designed as a result of the eutectic measurements by electrical resistivity. The information presented in the tables is for an 8-hr. single-shift operation and does not include the preparation and sterilization of the bulk solution or the filling operation.

It is apparent that the present cycle could be completed in less time if additional automatic controls were employed or if the plant operation was on a multishift basis. Nevertheless, even if the scheduling was optimized, freezing to a temperature of −40°, then drying at such a low temperature, would result in a longer drying time than where the product is frozen to −20° and dried. Since

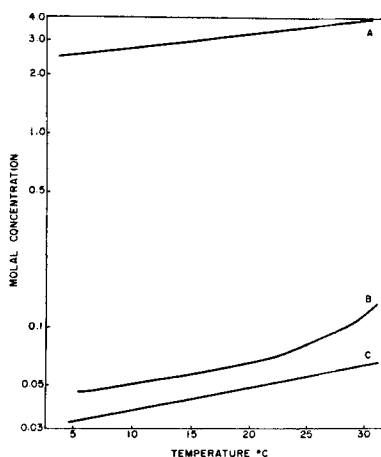Fig. 14.—Solubility of some salts of phentolamine as a function of temperature. Key: A, phentolamine methanesulfonate (−11.0°C.); B, phentolamine phosphate (−1.3°C.); C, phentolamine hydrochloride (−0.75°C.).

TABLE II.—PRESENT CYCLE FOR LYOPHILIZATION OF A PRODUCT HAVING A EUTECTIC TEMPERATURE
AT −12°C.

Day	Time	Description	Elapsed Time, hr.
1	2:30 p.m.	Chamber loaded and freezing initiated.	...
		Product frozen overnight to a temperature of −40°C.	
2	8:00 a.m.	Vacuum applied. Cellosolve circulated at 15°C.	17.5
2	4:30 p.m.	Heating of cellosolve discontinued.	26
3	3:30 a.m.	Heat to cellosolve tank automatically applied at a temperature of 50°C.	37
3	12:30 p.m.	Vacuum broken and product removed.	46
		Pressure reaches a maximum of 200 μ (−18° to −2°C.).	
		Total water removed, 9.5 L.	

TABLE III.—PROPOSED CYCLE FOR LYOPHILIZATION OF A PRODUCT HAVING A EUTECTIC TEMPERATURE
AT −12°C.

Day	Time	Description	Elapsed Time, hr.
1	2:00 p.m.	Chamber loaded and freezing initiated.	...
1	4:00 p.m.	Product at −25°C. Heat applied to shelves to warm product to −20°C.	2.5
1	5:00 p.m.	Vacuum applied. Cellosolve circulated at 65°C.	3.0
2	2:00 a.m.	Heat reduced to 50°C.	12.0
2	10:00 a.m.	Vacuum broken and product removed.	20.0
		Pressure reaches a maximum of 210 μ (−16° to −2°C.).	
		Total water removed, 9.5 L.	

the thermal conductance of the frozen mass is increased at the higher temperature, it is possible to apply a considerably greater amount of heat to the product frozen to −20°, thereby decreasing the drying time.

It is evident from the data presented in Tables II and III that considerable time can be saved in the lyophilization of pharmaceuticals by developing a cycle utilizing the accurate eutectic temperature obtained from resistivity measurements. It must be remembered, however, that although the eutectic temperature governs the temperature at which drying should be carried out, there are other factors which also are important. These factors are the supercooling effect and the thermal conductive property of the frozen mass. For some products, the supercooling effect may be of sufficient magnitude to upset the design of a cycle based solely on a knowledge of the eutectic temperature. For example, if a product has a eutectic point at −10° and shows a supercooling effect of approximately 10°, then to begin drying between −10° and −20° will result in considerable variation in the appearance of the dry product. The high internal pressure of the supercooled liquid in the sample causes frothing to occur or the cake to rise in the vial when vacuum is applied to the chamber. Consequently, for this product it would be necessary to freeze to below −20°, then allow the product to warm to −15° prior to application of vacuum.

SUMMARY

This investigation has illustrated that through precise eutectic temperature measurements, more efficient lyophilization cycles can be developed. This was accomplished with a specially designed low-conductivity bridge capable of measuring eutectic temperature accurately. The conductivity behavior for six organic electrolytes and three inorganic electrolytes has been investigated. Eutectic temperatures for the organics were found to be higher than those previously determined by time-temperature measurements, ranging from −0.75° to −12°. Higher eutectic temperatures for sodium chloride, potassium chloride, and potassium bromide were found to be in accord with previously reported values. The supercooling effect was illustrated and its significance discussed. Preliminary findings indicate that commonly used diluents, such as lactose and mannitol, have no effect on the eutectic temperature of organic medicinal agents.

The relationship between the solubility of a compound and its eutectic point has been demonstrated. An equation was derived which permits an estimation of the eutectic temperature from solubility information and melting point. The calculated values for the agents used in this study are, for the most part, in good agreement with the experimentally determined values.

An example is presented which demonstrates the utilization of conductivity information for designing a more efficient lyophilization cycle for a product currently in production.

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